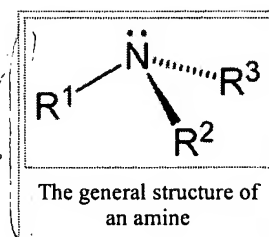


# Amine

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**Amines** are organic compounds and a type of functional group that contain nitrogen as the key atom. Structurally amines resemble ammonia, wherein one or more hydrogen atoms are replaced by organic substituents such as alkyl and aryl groups. An important exception to this rule is that compounds of the type  $RC(O)NR_2$ , where the  $C(O)$  refers to a carbonyl group, are called amides rather than amines. Amides and amines have different structures and properties, so the distinction is chemically important. Somewhat confusing is the fact that amines in which an N-H group has been replaced by an N-M group (M = metal) are also called amides. Thus  $(CH_3)_2NLi$  is lithium dimethylamide.



Amines are central in organic chemistry, all life processes known, as the core part of amino acids.

See the Category:Amines for a list of types of amine and some real examples of this class of chemical.

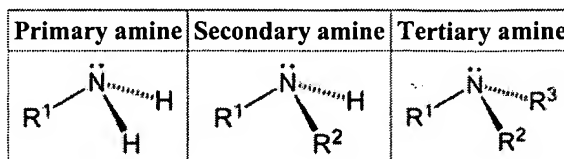
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## Introduction

### Aliphatic Amines

As displayed in the images below, **primary amines** arise when one of three hydrogen atoms in ammonia is replaced by an organic substituent. **Secondary amines** have two organic substituents bound to N together with one H. In **tertiary amines** all three hydrogen atoms are replaced by organic substituents. Note: the subscripts on the **R** groups are simply used to differentiate the organic substituents. However, the number subscripts on the H atoms show how many H atoms there are in that group. It is also possible to have four alkyl substituents on the nitrogen. These compounds have a charged nitrogen center, and necessarily come with a negative counterion, so they are called quaternary ammonium salts.



Similarly, an organic compound with multiple amino groups is called a **diamine**, **triamine**, **tetraamine** and so forth.

### Aromatic amines

Aromatic amines have the nitrogen atom connected to an aromatic ring as in anilines. The aromatic ring strongly decreases the basicity of the amine, depending on its substituents. Interestingly, the presence of an amine group strongly increases the

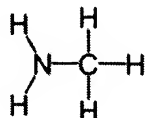
reactivity of the aromatic ring, due to an electron-donating effect. One organic reaction involving aromatic amines is the Goldberg reaction.

## Naming conventions

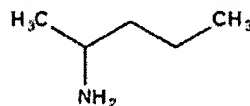
- the prefix "N-" shows substitution on the nitrogen atom
- as prefix: "amino-"
- as suffix: "-amine"
- remember that chemical compounds are not proper nouns, so lower case is indicated throughout.

Systematic names for some common amines:

Lower amines are named with the suffix *-amine*. Higher amines have the prefix *amino* as a functional group.



methylamine



2-aminopentane

(or sometimes: *pent-2-yl-amine* or *pentane-2-amine*)

- Primary amines:**
  - methylamine
  - ethanolamine or 2-aminoethanol
  - trisamine (or more commonly tris) (Its HCl salt is used as a pH buffering agent in biochemistry)
- Secondary amines:**
  - dimethylamine
  - methylethanolamine or 2-(methylamino)ethanol
- Cyclic amines:**
  - aziridine (3-member ring),
  - azetidine (4-member ring),
  - pyrrolidine (5-member ring) and
  - piperidine (6-member ring)
- Tertiary amines:**
  - trimethylamine
  - methyldiethanolamine (MDEA)
  - dimethylethanolamine (DMEA) or 2-(dimethylamino)ethanol
  - bis-tris (It is used as a pH buffering agent in biochemistry)

## Physical properties

### General properties

- Hydrogen bonding significantly influences the properties of primary and secondary amines as well as the protonated derivatives of all amines. Thus the boiling point of amines is higher than those for the corresponding phosphines, but generally lower than the corresponding alcohols. Alcohols, or alkanols, resemble amines but feature an -OH group in place of  $\text{NR}_2$ . Since oxygen is more electronegative than nitrogen,  $\text{RO-H}$  is typically more acidic than the related  $\text{R}_2\text{N-H}$  compound.
- Methyl-, dimethyl-, trimethyl-, and ethylamine are gases under standard conditions, while diethylamine and triethylamine are liquids. Most other common alkyl amines are liquids; high molecular weight amines are, of course, solids.
- Gaseous amines possess a characteristic ammonia smell, liquid amines have a distinctive "fishy" smell.
- Most aliphatic amines display some solubility in water, reflecting their ability to form hydrogen bonds. Solubility decreases with the increase in the number of carbon atoms, especially when the carbon atom number is greater than 6.
- Aliphatic amines display significant solubility in organic solvents, especially polar organic solvents. Primary amines react with ketones such as acetone, and most amines are incompatible with chloroform and carbon tetrachloride.
- The aromatic amines, such as aniline, have their lone pair electrons conjugated into the benzene ring, thus their tendency to engage in hydrogen bonding is diminished. Otherwise they display the following properties:
  - Their boiling points are usually still high due to their larger size.
  - Diminished solubility in water, although they retain their solubility in suitable organic solvents only.
  - They are toxic and are easily absorbed through the skin: thus hazardous.

## Chirality

Tertiary amines of the type  $\text{NHRR}'$  and  $\text{NRR}'\text{R}''$  are chiral: the nitrogen atom bears four distinct substituents counting the lone pair. The energy barrier for the inversion of the stereocenter is relatively low, e.g.  $\sim 7$  kcal/mol for a trialkylamine. The interconversion of the stereoisomers has been compared to the inversion of an open umbrella in to a strong wind. Because of this low barrier, amines such as  $\text{NHRR}'$  cannot be resolved optically and  $\text{NRR}'\text{R}''$  can only be resolved when the R, R', and R'' groups are constrained in cyclic structures.

## Properties as bases

Like ammonia, amines act as bases and are reasonably strong (see table for examples of conjugate acid  $K_a$  values). The basicity of amines depends on:

1. The availability of the lone pair of electrons on the Nitrogen atom.
2. The electronic properties of the substituents (alkyl groups enhance the basicity, aryl groups diminish it).
3. The degree of solvation of the protonated amine.

The nitrogen atom features a lone electron pair that can bind  $\text{H}^+$  to form an ammonium ion  $\text{R}_3\text{NH}^+$ . The lone electron pair is represented in this article by a two dots above or next to the N. The water solubility of simple amines is largely due to hydrogen bonding between protons on the water molecules and these lone electron pairs.

### ■ Inductive effect of alkyl groups

Ions of compound	$K_b$
Ammonia $\text{NH}_3$	$1.8 \cdot 10^{-5} \text{ M}$
Methylamine $\text{CH}_3\text{NH}_2$	$4.4 \cdot 10^{-4} \text{ M}$
propylamine $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	$4.7 \cdot 10^{-4} \text{ M}$
2-propylamine $(\text{CH}_3)_2\text{CHNH}_2$	$5.3 \cdot 10^{-4} \text{ M}$
diethylamine $(\text{CH}_3)_2\text{NH}$	$9.6 \cdot 10^{-4} \text{ M}$

+I effect of alkyl groups raises the energy of the lone pair of electrons, thus elevating the basicity.

### ■ Mesomeric effect of aromatic systems

Ions of compound	$K_b$
Ammonia $\text{NH}_3$	$1.8 \cdot 10^{-5} \text{ M}$
Aniline $\text{C}_6\text{H}_5\text{NH}_2$	$3.8 \cdot 10^{-10} \text{ M}$
4-methylphenylamine 4- $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	$1.2 \cdot 10^{-9} \text{ M}$

+M effect of aromatic ring delocalise the lone pair electron into the ring, resulting in decreased basicity.

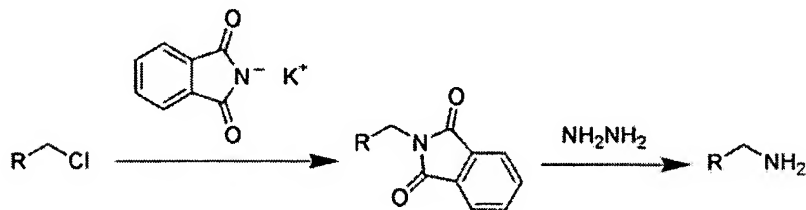
The degree of protonation of protonated amines:

Ions of compound	Maximum number of H-bond
$\text{NH}_4^+$	4 Very Soluble in $\text{H}_2\text{O}$
$\text{RNH}_3^+$	3
$\text{R}_2\text{NH}_2^+$	2
$\text{R}_3\text{NH}^+$	1 Least Soluble in $\text{H}_2\text{O}$

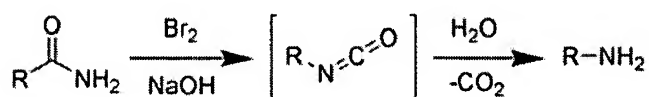
## Synthesis

The following laboratory methods exist for the preparation of amines:

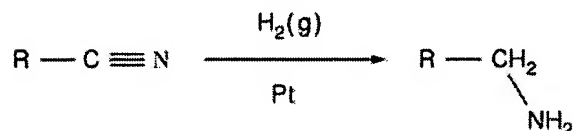
- via the Gabriel synthesis:



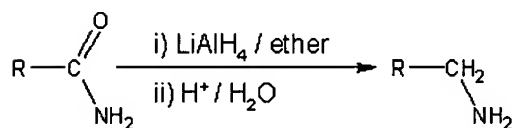
- via azides by the Staudinger reduction.
- From carboxylic acids in the Schmidt reaction.
- Allylic amines can be prepared from imines in the Aza-Baylis-Hillman reaction.
- via Hofmann degradation of amides. This reaction is valid for preparation of primary amines only. Gives good yields of primary amines uncontaminated with other amines.



- Quaternary ammonium salts upon treatment with strong base undergo the so-called Hofmann Elimination
- Reduction of nitriles, amides and nitro compounds:

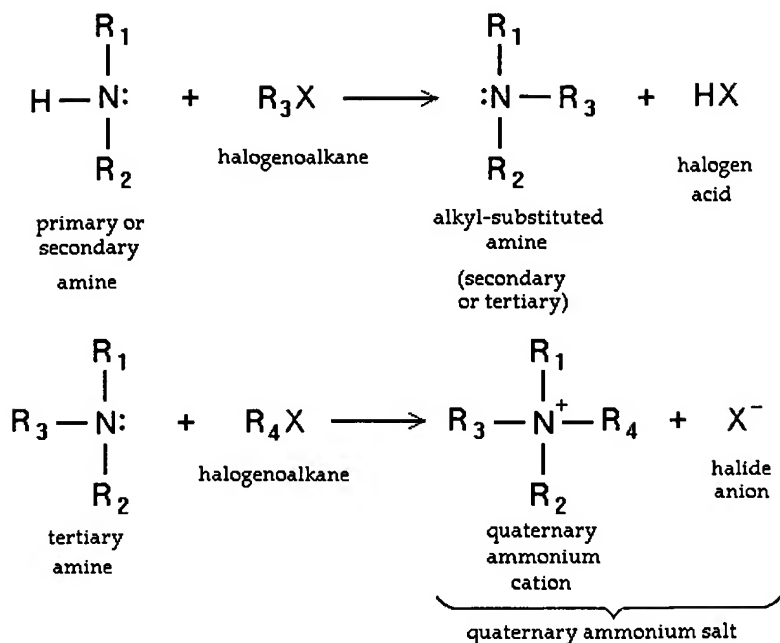


Nitriles are reduced to amines using hydrogen in the presence of a nickel catalyst, although acidic or alkaline conditions should be avoided to avoid hydrolysis of -CN group.  $\text{LiAlH}_4$  is more commonly employed for the reduction of nitriles on the laboratory scale. Similarly,  $\text{LiAlH}_4$  reduces amides to amines:



The reduction of nitro compounds to amines can be accomplished with elemental zinc, tin or iron with an acid.  
For more details on this topic, see *Reduction of nitro compounds*.

- Nucleophilic substitution of haloalkanes. Primary amines can also be synthesized by alkylation of ammonia. Haloalkanes react with amines to give a corresponding alkyl-substituted amine, with the release of a halogen acid. Such reactions, which are most useful for alkyl iodides and bromides, are rarely employed because the degree of alkylation is difficult to control. If the reacting amine is tertiary, a quaternary ammonium cation results. Many quaternary ammonium salts can be prepared by this route with diverse R groups and many halide and pseudohalide anions.

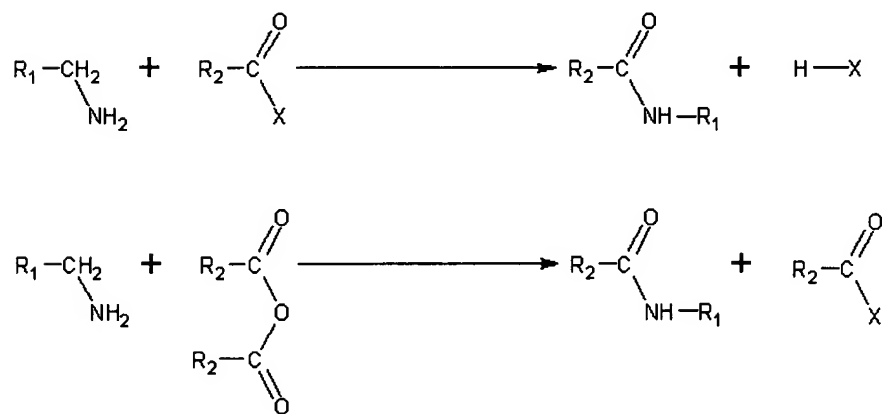


- via halides and hexamine in the Delepine reaction
- aryl amines can be obtained from amines and aryl halides in the Buchwald-Hartwig reaction
- from alkenes and alkynes in hydroamination

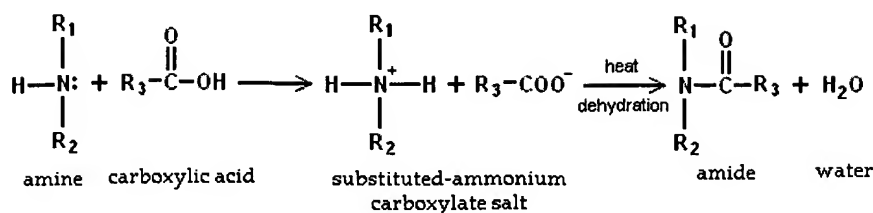
## Reactions

Amines react in a variety of ways:

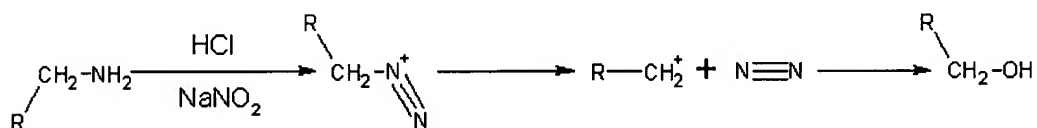
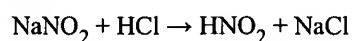
- By nucleophilic acyl substitution. Acyl chlorides and acid anhydrides react with primary and secondary amines in cold to form amides in the Schotten-Baumann reaction. Tertiary amines cannot be acylated due to the absence of a replaceable hydrogen atom. With the much less active benzoyl chloride, acylation can still be performed by the use of excess aqueous alkali to facilitate the reaction.



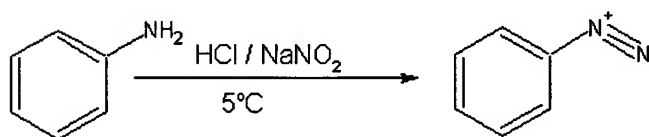
Because amines are basic, they neutralize carboxylic acids to form the corresponding ammonium carboxylate salts. Upon heating to 200 °C, the primary and secondary amine salts dehydrate to form the corresponding amides.



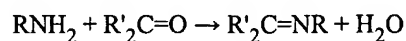
- By ammonium salt formation. Amines  $\text{R}_3\text{N}$  react with strong acids such as hydroiodic acid, hydrobromic acid and hydrochloric acid in neutralization reactions forming ammonium salts  $\text{R}_3\text{NH}^+$ .
- By diazonium salt formation. Nitrous acid with formula  $\text{HNO}_2$  is unstable, therefore usually a mixture of  $\text{NaNO}_2$  and dilute hydrochloric acid or sulfuric acid is used to produce nitrous acid indirectly. Primary aliphatic amines with nitrous acid give very unstable diazonium salts which spontaneously decompose by losing  $\text{N}_2$  to form carbonium ion. The carbonium ion goes on to produce a mixture of alkenes, alkanols or alkyl halides, with alkanols as the major product. This reaction is of little synthetic importance because the diazonium salt formed is too unstable, even at cold conditions.



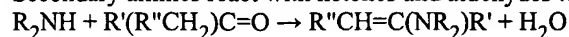
Primary aromatic amines, such as aniline (phenylamine) form more stable diazonium ions at 0–5 °C. Above 5 °C, they will decompose to give phenol and  $\text{N}_2$ . Arenediazonium salts can be isolated in the crystalline form but are usually used in solution immediately after preparation, due to rapid decomposition on standing even when cold. The solid arenediazonium salt is explosive upon shock or mild warming. Because of their greater stability, arenediazonium salts are more synthetically useful than their aliphatic counterparts. Since it is not necessary to isolate the diazonium salt, once it is formed another reagent such as cuprous cyanide can simply be added to the mixture, and with gentle heating of the solution, a replacement reaction takes place along with the evolution of nitrogen. In addition, arenediazonium ions can also undergo a coupling reaction with a highly activated aromatic compound such as a phenol to form an azo compound.



- By imine formation. Primary amines react with ketones and aldehydes to form imines. In the case of formaldehyde ( $\text{R}' = \text{H}$ ), these products are typically cyclic trimers.



Secondary amines react with ketones and aldehydes to form enamines



- By oxidation to nitroso compounds, for instance with peroxymonosulfuric acid.
- By reduction of quaternary ammonium cations to tertiary amines in the Emde degradation.
- By rearrangement of N-alkyl anilines to aryl substituted anilines in the Hofmann-Martius rearrangement.
- primary and secondary amines react with pyridinium salts in the Zincke reaction

## Biological activity

Amines have strong, characteristic, disagreeable odors, and are toxic. The smells of ammonia, fish, urine, rotting flesh and semen are all mainly composed of amines. Many kinds of biological activity produce amines by breakdown of amino acids.

## Use of amines

### Dyes

Primary aromatic amines are used as a starting material for the manufacture of azo dyes. It reacts with nitric(III) acid to form diazonium salt which can undergo coupling reaction to form azo compound. As azo-compounds are highly coloured, they are widely used in dyeing industries, such as:

- Methyl orange
- Direct brown 138
- Sunset yellow FCF
- Ponceau

### Drugs

- Chlorpheniramine is an antihistamine that helps to relieve allergic disorders due to cold, hay fever, itchy skin, insect bites and stings.
- Chlorpromazine is a tranquillizer that sedates without inducing sleep. It is used to relieve anxiety, excitement, restlessness or even mental disorder.
- Ephedrine and Phenylephrine, as amine hydrochlorides, are used as decongestants.
- Amphetamine, Methamphetamine, and Methcathinone are amines that are listed as controlled substances by the DEA.
- Amitriptyline, Imipramine, Lofepramine and Clomipramine are tricyclic antidepressants and tertiary amines
- Nortriptyline, Desipramine, and Amoxapine are tricyclic antidepressants and secondary amines
- (The tricyclics are grouped by the nature of the final amine group on the side chain.)

### Gas Treatment

- Aqueous monoethanolamine (MEA), diglycolamine (DGA), diethanolamine (DEA), diisopropanolamine (DIPA) and methyldiethanolamine (MDEA) are widely used industrially for removing carbon dioxide (CO<sub>2</sub>) and hydrogen sulphide (H<sub>2</sub>S) from natural gas streams and refinery process streams. They may also be used to remove CO<sub>2</sub> from combustion gases / flue gases and may have potential for abatement of greenhouse gases.

## See also

- IUPAC nomenclature for the official naming rules for amines.
- Biogenic amine
- Acid-base extraction
- Amine gas treating

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Category: Amines

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# Amide

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In chemistry, an **amide** is one of two kinds of compounds: ?

- the organic functional group characterized by a carbonyl group (C=O) linked to a nitrogen atom (N), of a compound that contains this functional group (pictured to the right), or
- a particular kind of nitrogen anion.

Amides are the most stable of all the carbonyl functional groups.

Many chemists make a pronunciation distinction between the two, saying (IPA: [ə'mɪd] for the carbonyl-nitrogen compound and ['æməɪd] for the anion. Others substitute one of these pronunciations with ['æmɪd], while still others pronounce both as ['æmɪd], making them homonyms.

In the first sense referred to above, an amide is an amine where one of the nitrogen substituents is an acyl group; it is generally represented by the formula:  $R_1(CO)NR_2R_3$ , where either or both  $R_2$  and  $R_3$  may be hydrogen. Specifically, an amide can also be regarded as a derivative of a carboxylic acid in which the hydroxyl group has been replaced by an amine or ammonia.

Compounds in which a hydrogen atom on nitrogen from ammonia or an amine is replaced by a metal cation are also known as amides or **azanides**.

The second sense of the word *amide* is the amide anion, which is a deprotonated form of ammonia (NH<sub>3</sub>) or an amine. It is generally represented by the formula:  $[R_1NR_2]^-$ , and is an extremely strong base, due to the extreme weakness of ammonia and its analogues as Brønsted acids.

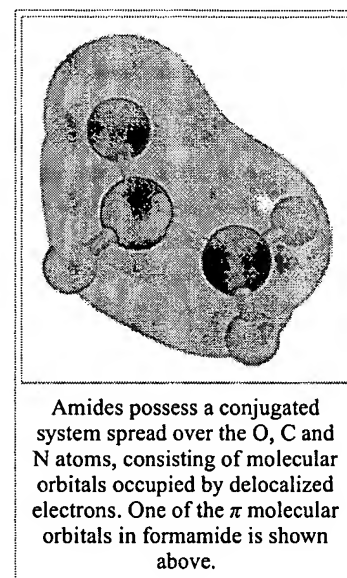
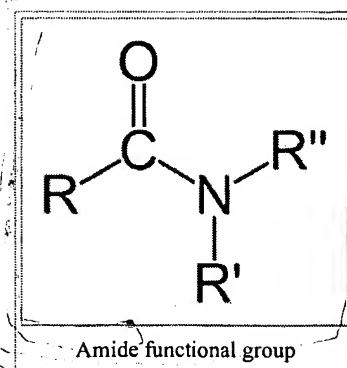
The remainder of this article is about the carbonyl-nitrogen sense of *amide*. For examples of the anionic amide, see the articles Sodium amide and Lithium diisopropylamide.

## Contents

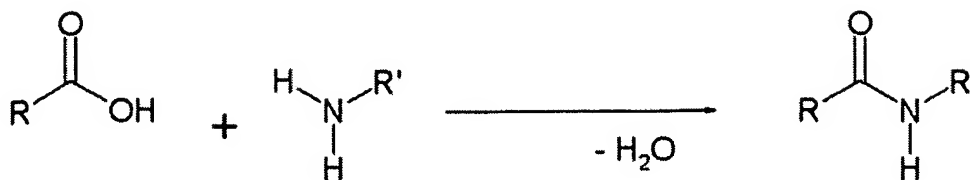
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## Amide synthesis

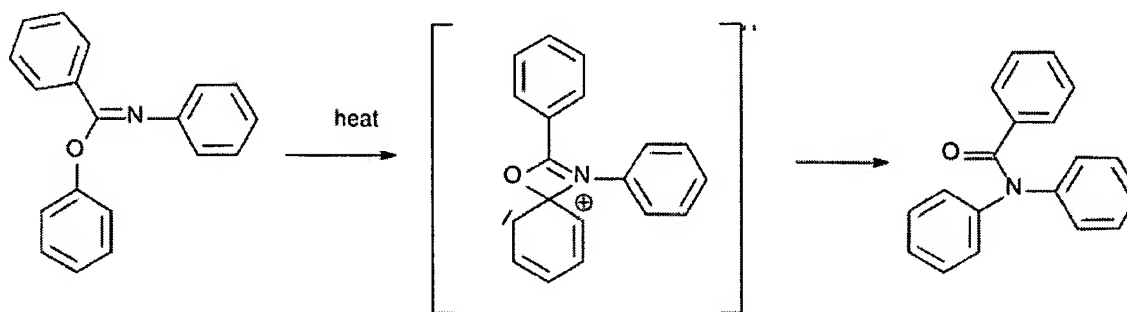
- Amides are commonly formed from the reaction of a carboxylic acid with an amine. This is the reaction that forms peptide bonds between amino acids. These amides can participate in hydrogen bonding as hydrogen bond acceptors and donors, but do not ionize in aqueous solution, whereas their parent acids and amines are almost completely ionized in solution at neutral pH. Amide formation plays a role in the synthesis of some condensation polymers, such as nylon and Aramid (Twaron / Kevlar). In biochemistry peptides are synthesized in solid phase peptide synthesis. The Schotten-Baumann reaction describes the formation of amides from amines and acid chlorides.







- Cyclic amides are synthesized in the Beckmann rearrangement from oximes.
- Amides also form ketones in the Schmidt reaction
- Amides can be prepared from aryl alkyl ketones, sulfur and morpholine in the Willgerodt-Kindler reaction
- Other amide-forming reactions are the Passerini reaction and the Ugi reaction
- In the **Bodroux reaction** an amide  $\text{RNHCOR}'$  is synthesized from a carboxylic acid  $\text{R}-\text{COOH}$  and the adduct of a Grignard reagent with an aniline derivative  $\text{ArNHR}'$  [1] [2]
- In the **Chapman rearrangement** (first reported in 1925) an aryl imino ester is converted to a N,N-diaryl amide:



The reaction mechanism is based on a nucleophilic aromatic substitution. [3]

## Amide reactions

- Amide breakdown is possible via amide hydrolysis. Such hydrolysis can occur under basic or acidic conditions. Acidic conditions yield the carboxylic acid and the ammonium ion while basic hydrolysis yield the carboxylate ion and ammonia.
- In the Vilsmeier-Haack reaction an amide is converted into an imine.
- Hofmann rearrangement of primary amides to primary amines.

Owing to their resonance stabilization, amides are relatively unreactive under physiological conditions, even less than similar compounds such as esters. Nevertheless, amides can undergo chemical reactions, usually through an attack of an electronegative atom on the carbonyl carbon, breaking the carbonyl double bond and forming a tetrahedral intermediate. When the functional group attacking the amide is a thiol, hydroxyl or amine, the resulting molecule may be called a cyclol or, more specifically, a thiacyclol, an oxacyclol or an azacyclol, respectively.

The proton of an amide does not dissociate readily under normal conditions; its  $\text{p}K_a$  is usually well above 15. However, under extremely acidic conditions, the carbonyl oxygen can become protonated with a  $\text{p}K_a$  of roughly -1.

Amides will react with nitrous acid ( $\text{HONO}$ ) forming the carboxylic acid and yielding nitrogen. Nitrous acid is formed by addition of a strong acid to a nitrate (III) salt in solution at temperatures of between 0 and 10 degrees.

Amides undergo Hofmann's degradation reaction in which an amide yields an amine with one less carbon atom upon reaction with bromine and sodium hydroxide. One should also note that reacting the amide with the strong reducing agent lithium tetrahydridoaluminate yields an amine with the same number of carbon atoms.

Amides are dehydrated with phosphorus (V) oxide forming the nitrile. Care should be taken when performing such a reaction since phosphorus (V) oxide smoulders when in contact with organic matter.

## Amide linkage (peptide bond)

An amide linkage is kinetically stable to hydrolysis. However, it can be hydrolysed in boiling alkali, as well as in strong acidic conditions. Amide linkages in a biochemical context are called peptide linkages. Amide linkages constitute a defining molecular

feature of proteins, the secondary structure of which is due in part to the hydrogen bonding abilities of amides.

## Amide properties

Compared to amines, amides are very weak bases. While the conjugate acid of an amine has a pK<sub>a</sub> of about 9.5, the conjugate acid of an amide has a pK<sub>a</sub> around -0.5. Therefore amides don't have as clearly noticeable acid-base properties in water. This lack of basicity is explained by the electron-withdrawing nature of the carbonyl group where the lone pair of electrons on the nitrogen is delocalized by resonance, thus forming a partial double bond with the carbonyl carbon and putting a negative charge on the oxygen. On the other hand,

amides are much stronger bases than carboxylic acids, esters, aldehydes, and ketones (conjugated acid pK<sub>a</sub> between -6 and -10). It is estimated in silico that acetamide is represented by resonance structure A for 62% and by B for 28% <sup>[4]</sup>. Resonance is largely prevented in the very strained quinuclidone.



## Solubility

Amides contain carbonyl (C=O) and ether (N-C) dipoles arising from covalent bonding between electronegative oxygen and nitrogen atoms and electro-neutral carbon atoms. Primary and secondary amides also contain two- and one N-H dipoles, respectively. Because of the pi-bonding arrangement of the carbonyl and the greater electronegativity of oxygen, the carbonyl (C=O) is a stronger dipole than the N-C dipole. The presence of a C=O dipole and, to a lesser extent a N-C dipole, allows amides to act as H-bond acceptors. In primary and secondary amides, the presence of N-H dipoles allows amides to function as H-bond donors as well. Thus amides can participate in hydrogen bonding with water and other protic solvents; the oxygen and nitrogen atoms can accept hydrogen bonds from water and the N-H hydrogen atoms can donate H-bonds. As a result of interactions such as these, the water solubility of amides is greater than that of corresponding hydrocarbons

While hydrogen bonding may enhance the water solubility of amides relative to hydrocarbons (alkanes, alkenes, alkynes and aromatic compounds), amides typically are regarded as compounds with low water solubility. They are significantly less water soluble than comparable acids or alcohols due to: 1). their non-ionic character 2). the presence of nonpolar hydrocarbon functionality, and 3). the inability of tertiary amides to donate hydrogen bonds to water (they can only be H-bond acceptors). Thus amides have water solubilities roughly comparable to esters. Typically amides are less soluble than comparable amines and carboxylic acids since these compounds can both donate and accept hydrogen bonds, and can ionize at appropriate pHs to further enhance solubility

## Derivatives

Sulfonamides are analogues of amides in which the atom double-bonded to oxygen is sulfur rather than carbon.

Cyclic amides are called lactams.

## Naming conventions

- Example: CH<sub>3</sub>CONH<sub>2</sub> is named acetamide or ethanamide
- Other examples: propan-1-amide, N,N-dimethylpropanamide, acrylamide
- For more detail see IUPAC nomenclature of organic chemistry - Amines and Amides

## References

1. ^ Bodroux F., Bull. Soc. Chim. France, 1905, 33, 831;
2. ^ Bodroux reaction at the Institute of Chemistry, Skopje, Macedonia Link
3. ^ *Advanced organic Chemistry, Reactions, mechanisms and structure* 3ed. Jerry March ISBN 0-471-85472-7
4. ^ "Amide Resonance" *Correlates with a Breadth of C-N Rotation Barriers* Carl R. Kemnitz and Mark J. Loewen J. Am. Chem. Soc.; 2007; 129(9) pp 2521 - 2528; (Article) doi:10.1021/ja0663024

## External links

- IUPAC Compendium of Chemical Terminology

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Categories: Amides | Functional groups

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